

REMARKS

Claims 1-3, 7-11, 13, 14, 17, 18, 33-35, 39, 41, 43, 44 and 47 are pending, with claims 1-3, 7-11, 14, 14, 17 and 18 withdrawn from consideration. Applicants have hereinabove canceled claims 1-3, 7-11, 13, 14, 17, 18, 34, 35 and 43 without prejudice or disclaimer to applicants' right to pursue the subject matter of these claims in the future. In addition, applicant has amended claims 33, 39 and 47 and added new claims 81-89. Applicants note that new claims 81-89 read on the species nucleic acid, the species plastic and the species bead as elected in applicants' response to the September 19, 2006 Restriction Requirement filed by applicants on December 15, 2006.

Support for the amendments to claim 33 can be found in the specification as originally filed at, inter alia, page 12, lines 6-14; page 13, lines 9-10; page 7, lines 14-18; and page 8, lines 3-5. Support for the amendments to claim 39 can be found in the specification as originally filed at, inter alia, page 12, line 29 to page 13, line 1. Support for the amendments to claim 47 can be found in the specification as originally filed at, inter alia, page 12, lines 15-23; page 13, lines 9-10 page 7, lines 14-18; and page 8, lines 3-5. Support for new claim 81 can be found in the specification as originally filed at, inter alia, page 12, line 29 to page 13, line 1. Support for new claim 82 can be found in the specification as originally filed at, inter alia, page 13, lines 1-4. Support for new claim 83 can be found in the specification as originally filed at, inter alia, page 22, lines 1-5; page 23, lines 11-23. Support for new claim 84 can be found in the specification as originally filed at, inter alia, page 11, lines 22-24. Support for new claim 85 can be found in the specification as originally filed at, inter alia, page 22, lines 1-10. Support for new claim 86 can be found in the specification as originally filed at, inter alia, page 22, lines 1-10. Support for new claim 87 can be found in the specification as originally

filed at, inter alia, page 22, lines 1-5 and 10-11. Support for new claim 88 can be found in the specification as originally filed at, inter alia, page 22, lines 1-11. Support for new claim 89 can be found in the specification as originally filed at, inter alia, page 22, lines 1-11. Applicants maintain that this amendment raises no issue of new matter. Accordingly, applicants respectfully request entry of this Amendment.

Information Disclosure Statements

In the February 15, 2007 Office Action the Examiner stated that a listing of references in the specification is not a proper information disclosure statement.

Applicants refer the Examiner to the Information Disclosure Statements filed June 1, 2004 and September 8, 2004 and the Supplemental Information Disclosure Statement filed herewith.

Sequence Listing

The Examiner indicated that page 15 and Figs. 1, 3, 5 and 11 contain unidentified sequences. A copy of the Notice to Comply issued with the Office Action is attached hereto as **Exhibit A**.

In response, applicants have hereinabove amended the specification including the Brief Description of the Figures, to recite the necessary sequence identifiers as necessary. In addition, applicants request that the current Sequence Listing be replaced with the paper copy Sequence listing attached hereto as **Exhibit B**. Applicants note that the replacement Sequence Listing does not contain any new matter. In addition, applicants attach hereto as **Exhibit C** a Statement in Accordance with 37 C.F.R. §1.821(f) and a computer readable format Sequence Listing as **Exhibit D**. Accordingly, applicants respectfully request that the

Examiner reconsider and withdraw this ground of rejection.

Rejections Under 35 U.S.C. §103(a)

Claims 33-35, 39, 41 and 47

The Examiner rejected claims 33-35, 39, 41 and 47 as allegedly obvious over Kolb et al. (Agnew Chem. Int. Ed. 2001, 40:2001-2021) and Konrad et al. (U.S. Patent No. 5,789,167, issued August 1, 1998). The Examiner asserted that Kolb et al. do not specifically teach linking biomolecules to a solid surface or where the solid surface is plastic beads, nor do they teach DNA as the biomolecule. The Examiner further asserted that Kolb et al. teach a method of 1,3-dipolar cycloaddition between azido and alkynyl groups thereby covalently linking two molecules together. The Examiner asserted that Kolb et al. teach biomolecules where the biomolecule is a nucleic acid (see Abstract). The Examiner also asserted that Konrad do not teach a 1,3-dipolar cycloaddition reaction between azido and alkynyl groups but do teach where the biomolecule is a nucleic acid and is DNA and teach where DNA oligonucleotides are covalently bound to plastic beads. The Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the method of Kolb et al. by immobilizing plastic beads on DNA as suggested by Konrad et al. The Examiner asserted that the motivation to do so is provided by Konrad et al. which teach "the method can be used for mapping, for identity typing, and to determine whether a test oligonucleotide sequence is present in the sample".

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicants have herein amended independent claim 33, from which claims 39, 41 and new claims 87-89 depend, and have amended independent claim 47, from which new claims 81-86 depend. Applicants note

that the Examiner asserted that one of skill in the art would use the click chemistry method of Kolb et al. to immobilize DNA on a solid surface (plastic beads) as suggested by Konrad et al., and cites the uses of the method set forth in Konrad as the motivation to do so. However, applicant notes that Kolb et al. discusses the point of click chemistry as "joining *small* units together with heteroatom links (C-X-C)". In contrast, applicants' independent claims 33 and 47, as amended, recite affixing a deoxyribonucleic acid to a solid surface, i.e. a large molecule according to Kolb et al. (applicant notes that Kolb et al. characterizes polynucleotides as "large oligomers", see page 2-7, right hand column).

Moreover, with regard to the Examiner's statement, citing the Abstract, that "Kolb et al. teach biomolecules where the biomolecule is a nucleic acid" applicants note that if read in the context of the Abstract this statement refers to "small subunits stitched together by carbon-heteroatom bonds" (see Abstract of Kolb et al.). As the Examiner has stated, Kolb et al. do not specifically teach linking biomolecules to a solid surface, and, as applicants have pointed out, Kolb et al. discuss click chemistry with regard to small molecules. There is no suggestion that the method can be used for attaching large molecules to solid surfaces, and Konrad et al., notwithstanding the Examiner's asserted motivation recited therein, only discusses attaching oligonucleotides to a solid surface, not a reason to specifically use click chemistry to do such. Thus, there is no suggestion or concept in the combination of cited references of the invention as claimed. In addition, there is no suggestion in the art to use specific azide-alkynyl cycloaddition to affix a DNA to a solid surface. There is no teaching or suggestion in the combined references of the method as claimed in amended claims 33 and 47.

Applicants also assert, given the caution provided in Kolb et al. with regard to the physical hazards of organic azides in the presence of acetylenic groups (see page 2021, item [77] - referenced at page 2015), one of ordinary skill in the art would not chose azide-alkynyl cycloaddition to attach a DNA to a solid surface. Konrad et al. in combination with Kolb et al. does not suggest otherwise.

Accordingly, in light of the amendments made and arguments presented hereinabove, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 43 and 44

The Examiner rejected claims 43 and 44 as allegedly obvious over Kolb et al. (Agnew Chem. Int. Ed. 2001, 40:2001-2021) and Konrad et al. (U.S. Patent No. 5,789,167, issued August 1, 1998) in view of Lewis et al. (Agnew Chem. Int. Ed. 2002, 41(6):1053-1057). The Examiner asserted that Lewis et al. teach a method wherein the conditions permitting a 1,3-dipolar cycloaddition to occur comprise contacting at room temperature and contacting in the presence of cucurbitril.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicants have herein amended independent claim 33, from which rejected claim 44 depends (claim 43 has been cancelled without prejudice). Applicants note that the Examiner asserted that one of skill in the art would use the click chemistry method of Kolb et al. to immobilize DNA on a solid surface (plastic beads) as suggested by Konrad et al., and cites the uses of the method set forth in Konrad as the motivation to do so. However, applicant notes that Kolb et al. discusses the point of click chemistry as "joining *small* units together with heteroatom links (C-X-C)". In contrast,

applicants' independent claim 33 as amended, recites affixing a deoxyribonucleic acid to a solid surface, i.e. a large molecule according to Kolb et al. (applicant notes that Kolb et al. characterizes polynucleotides as "large oligomers", see page 2-7, right hand column).

Moreover, with regard to the Examiner's statement, citing the Abstract, that "Kolb et al. teach biomolecules where the biomolecule is a nucleic acid" applicants note that if read in the context of the Abstract this statement refers to "small subunits stitched together by carbon-heteroatom bonds" (see Abstract of Kolb et al.). As the Examiner has stated, Kolb et al. do not specifically teach linking biomolecules to a solid surface, and, as applicants have pointed out, Kolb et al. discuss click chemistry with regard to small molecules. There is no suggestion that the method can be used for attaching large molecules to solid surfaces, and Konrad et al., notwithstanding the Examiner's asserted motivation recited therein, only discusses attaching oligonucleotides to a solid surface, not a reason to specifically use click chemistry to do such. Thus, there is no suggestion of the invention as claimed in the combination of cited references. In addition, there is no suggestion in the art of specific azide-alkynyl cycloaddition to affix a DNA to a solid surface. Lewis et al. in combination with Kolb et al. and Konrad et al. does not cure this deficiency. Dependent claim 44 includes all of the characteristics recited in claim 33 which are not suggested by the cited references in combination.

Also, as note above, given the caution provided in Kolb et al. with regard to the physical hazards of organic azides in the presence of acetylenic groups (see page 2021, item [77] - referenced at page 2015), one of ordinary skill in the art would not chose azide-alkynyl cycloaddition to attach a DNA to a solid

surface. Lewis et al. in combination with Konrad et al. and Kolb et al. do not suggest otherwise.

Claim 44

The Examiner rejected claim 44 as allegedly obvious over Kolb et al. (Agnew Chem. Int. Ed. 2001, 40:2001-2021) and Konrad et al. (U.S. Patent No. 5,789,167, issued August 1, 1998) in view of Jen et al. (American Chemical Society 9/26/2000). The Examiner stated that Jen et al. teach using organic catalysts for 1,3-dipolar cycloadditions.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicants have herein amended independent claim 33, from which rejected claim 44 depends. Applicants note that the Examiner asserted that one of skill in the art would use the click chemistry method of Kolb et al. to immobilize DNA on a solid surface (plastic beads) as suggested by Konrad et al., and cites the uses of the method set forth in Konrad as the motivation to do so. However, applicant notes that Kolb et al. discusses the point of click chemistry as "joining *small* units together with heteroatom links (C-X-C)". In contrast, applicants' independent claim 33 as amended, recites affixing a *DNA* to a solid surface, i.e. a large molecule according to Kolb et al. (applicant notes that Kolb et al. characterizes polynucleotides as "large oligomers", see page 2-7, right hand column).

Moreover, with regard to the Examiner's statement, citing the Abstract, that "Kolb et al. teach biomolecules where the biomolecule is a nucleic acid" applicants note that if read in the context of the Abstract this statement refers to "small subunits stitched together by carbon-heteroatom bonds" (see Abstract). As the Examiner has stated, Kolb et al. do not

specifically teach linking biomolecules to a solid surface, and, as applicants have pointed out, Kolb et al. discuss click chemistry with regard to small molecules. There is no suggestion that the method can be used for attaching large molecules to solid surfaces, and Konrad et al., notwithstanding the Examiner's asserted motivation recited therein, only discusses attaching oligonucleotides to a solid surface, not a reason to specifically use click chemistry to do such. Thus, there is no suggestion in the combination of cited references to use click chemistry, specifically azide-alkynyl cycloaddition, to affix a DNA to a solid surface. Also, Jen et al. in combination with Kolb et al. and Konrad et al. do not cure this deficiency. Applicant maintain that claim 44 recites characteristics not suggested by the cited references in combination.

Also, as note above, given the caution provided in Kolb et al. with regard to the physical hazards of organic azides in the presence of acetylenic groups (see page 2021, item [77] - referenced at page 2015), one of ordinary skill in the art would not chose azide-alkynyl cycloaddition to attach a DNA to a solid surface. Jen at al. in combination with Konrad et al. and Kolb et al. do not suggest otherwise.

Combination of References

In the February 15, 2007 Office Action, the Examiner combines the Kolb reference with the Konrad patent. Applicants submit there is no basis for the combination. The Kolb reference is a synthesis paper directed at accelerating "the discovery of substances with useful properties, new medicines being the example emphasized." (p.2017). There is nothing in the Kolb reference to suggest that the chemistry should be applied to *immobilization* problems. The Examiner acknowledges that the Kolb does "not specifically teach linking biomolecules to a solid surface . . ." (Office Action, p.6). The Examiner also notes that the Abstract of Kolb teaches

"biomolecules and where the biomolecule is a nucleic acid." (Office Action, p.6). This observation is not relevant to the present invention, however, because Kolb et al. are not proposing a new chemistry for *immobilizing* macromolecules (such as a nucleic acid); instead Kolb et al. are proposing a new chemistry for *generating* macromolecules using carbon-heteroatom bonds:

"We are proposing here the use of click reactions in combinatorial style generate molecules of highly diverse structure and function." (p.2011).

Thus, the Examiner has not indicated where in the references cited there is a suggestion to apply the technology to immobilization, and applicants find no suggestion in the references to do so.

With regard to the Konrad patent, the Examiner argues that Konrad teaches "where the DNA oligonucleotides are covalently bound to plastic beads . . ." (Office Action p.7). The Examiner points to column 28, line 44 through column 29, line 29. However, this section describes a completely different chemistry for attachment:

"Polystyrene beads 0.5 microns in diameter, containing internal green fluorescent dye and surface carboxyl groups were purchased from Duke Scientific Corp., Palo Alto, Calif. One ml of the 1 percent solid suspension supplied by the manufacturer was mixed with 300 .mu.l of a solution containing 5 mg/ml EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) and 1 mg/ml of sulfo-NHS (sulfo-N-hydroxy-succinimide, both purchased from Pierce Chemical Co., Rockford, Ill.) in 0.1M MOPS (4-morpholine propane sulfonic acid, Sigma Chemical Co., St. Louis, Mo.) at pH 7.5. To this mixture was added 60 .mu.l 1M NaCl, 15 .mu.l carrier DNA (degraded free acid from herring sperm, Cat. D3159, Sigma Chemical Co., St. Louis, Mo., at 100 mg/ml brought to pH 7 with NaOH), and 120 .mu.l water. Finally, 5 .mu.l of the oligonucleotide probe (0.45 mM in water) containing a 5' terminal primary amine group on a 12 carbon spacer (National Biosciences, Inc., Plymouth, Minn.) was added."

The Examiner argues that it would be obvious to modify the method of Kolb et al. by immobilizing DNA on plastic beads as suggested

by Konrad, because Konrad teaches the usefulness of mapping, identity typing, and the like. (Office Action p.7). Applicants note, however, that Konrad teaches the usefulness of the chemistry quoted hereinabove in the context of mapping, identity typing and the like - not the usefulness of the chemistry of Kolb et al. There is nothing in the Konrad patent that hints or suggests at the need to use a *different* chemistry, such as the click chemistry of Kolb. The Examiner has pointed to nothing in Konrad that substantiates a link to Kolb and has made a conclusory statement.

With regard to this last point, applicants respectfully direct the Examiner's attention to the recent Supreme Court opinion which says that a specific showing by the Examiner is required and that conclusory statements are not sufficient:

"Often, it will be necessary [...] to look to interrelated teachings of multiple patents [...] in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v. Teleflex, Slip Op No. 04-1350 (April 30, 2007). Here the Examiner has offered no rational underpinning to support the conclusion of obviousness. Rather than provide some indication from Konrad that he is seeking better chemistries, the Examiner has only provided a quote from Konrad that indicates Konrad thinks his chemistry is perfectly fine for his intended uses.

The remaining cited references do not cure these deficiencies in the Examiner's combination of Konrad and Kolb.

Accordingly, in light of the amendments made and arguments presented hereinabove, applicants respectfully request that the

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Examiner reconsider and withdraw this ground of rejection.